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(54) Hydrogenation of prochiral ketones

(57) Process for enantioselectively hydrogenating prochiralen ketones to (S)-alcohols using platinum catalysts in the presence of cinchonines or quinidines as modifiers and in the presence of hydrogen, which is characterized in that the modifiers used are cinchonines unsubstituted in the 3-position, 3-ethylidenyl- or 9-methoxycinchonines or derivatives thereof in which the quinoline ring is replaced by other rings.

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Description

[0001] The present invention relates to a process for enantioselectively hydrogenating prochiral ketones to (S)-alcohols using platinum catalysts in the presence of cinchonines or quinidines as modifiers and of hydrogen, which is characterized in that the modifiers used are cinchonines unsubstituted in the 3-position, 3-ethylidenyl- or 9-methoxycinchonines or derivatives thereof in which the quinoline ring is replaced by other rings.

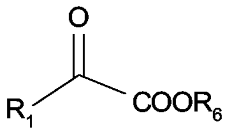
[0002] The enantioselective hydrogenation of α-ketoesters using platinum catalysts in the presence of cinchonidine or cinchonine and derivatives of these quinuclidines has been described by H.-U. Blaser et al. in Catalysis Today 37 (1997), pages 441 to 463. This publication also discloses that the enantioselectivity in the presence of cinchonidine for preparing (R)-alcohols is considerably higher than in the presence of cinchonine for preparing (S)-alcohols. The same observation is made by B. Török et al. in Chem. Comm. (1999), pages 1725 to 1726 in the enantioselective hydrogenation of an α-ketodiacetal. The hydrogenation of α-ketoacetals is also described by M. Studer et al. in Chem. Comm. (1999), pages 1727 to 1728. In J. Am. Chem. Soc. (2000) 122, pages 12675 to 12682, H.U. Blaser describes the influence of modification of cinchona alkaloids on the hydrogenation of ethyl pyruvate using cinchona-modified platinum catalysts. It is established that the substitution in the 3-position of the quinuclidine radical has virtually no or only a small influence. In connection with the determination of the pK_a values of cinchona alkaloids, C. Drzewiczak et al. in Polish J. Che., 67, 48ff (1993) mention 3-ethylidenecinchonine without specifying a synthesis or use.

[0003] It has now been found that, surprisingly, it is possible to achieve a distinctly higher catalyst activity and increased enantioselectivity in the hydrogenation of prochiral ketones to (S)-alcohols using hydrogen when platinum catalysts are modified with 3-ethylidene- or 9-methoxycinchonines or derivatives thereof in which the quinoline ring is replaced by other rings. The optical yields of (S)-alcohols may be over 90% ee and such high yields could hitherto be achieved in the preparation of (S)-alcohols by this hydrogenation route only by the use of ultrasound (B. Török et al., Ultrasonics Sonochemistry 7 (2000) 151) or by continuously adding modifier (C. LeBlond et al., JACS 121 (1999) 4920).

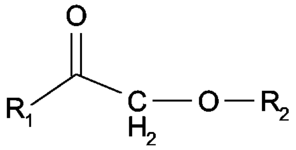
[0004] The invention provides a process for enantioselectively hydrogenating prochiralen ketones to (S)-alcohols using platinum catalysts in the presence of cinchonines or quinidines as modifiers and in the presence of hydrogen, which is characterized in that the modifiers used are cinchonines from the group of cinchonines unsubstituted in the 3-position, 3-ethylidenyl- or 9-methoxycinchonines or derivatives thereof in which the quinoline ring is replaced by other rings.

[0005] Prochiral ketones are well known. The prochiral α-ketones may be saturated or unsaturated, open-chain or cyclic compounds which preferably have 5 to 30, more preferably 5 to 20, carbon atoms which are unsubstituted or substituted with radicals which are stable under the hydrogenation conditions. The carbon chain may be interrupted by heteroatoms, preferably from the group of -O-, =N- and -NR'-, where R' is H, C_1-C_8-alkyl, preferably C_1-C_4-alkyl, C_5-C_8-cycloalkyl, for example cyclopentyl, cyclohexyl or cyclooctyl, C_6-C_{10}-aryl, for example phenyl or naphthyl, or C_7-C_{12}-aralkyl, for example phenylmethyl or phenylethyl. The prochiral ketones preferably have an activating group in the α-position, for example a carboxyl, carboxylic ester, acetal, keto or ether group.

[0006] The prochiralen ketones may be α-ketocarboxylic acids, α-ketocarboxylic esters, α-ketoethers, α-ketoacetals and α,β-diketones. These prochiral ketones may correspond to the formulae I, II, III, IV and V



(I)



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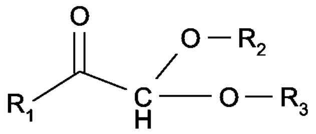

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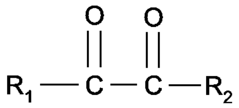
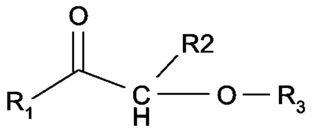


$$R_1-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle O}{\|}}{C}-R_2$$

(IV)



(V)

where

R_1, R_2, R_3 and R_6 are each independently a monovalent, saturated or unsaturated aliphatic radical having 1 to 12 carbon atoms, a saturated or unsaturated cycloaliphatic radical having 3 to 8 carbon atoms, a saturated or unsaturated heterocycloaliphatic radical having 3 to 8 ring members and one or two heteroatoms from the group of O, N and NR', a saturated or unsaturated cycloaliphatic-aliphatic radical having 4 to 12 carbon atoms, a saturated or unsaturated heterocycloaliphatic-aliphatic radical having 3 to 12 carbon atoms and one or two heteroatoms from the group of O, N and NR', an aromatic radical having 6 to 10 carbon atoms, a heteroaromatic radical having 4 to 9 carbon atoms and one or two heteroatoms from the group of O and N, an aromatic-aliphatic radical having 7 to 12 carbon atoms or a heteroaromatic-aliphatic radical having 5 to 11 carbon atoms and one or two heteroatoms from the group of O and N where R' is H, C_1-C_8-alkyl, preferably C_1-C_4-alkyl, C_5- or C_6-cycloalkyl, C_6-C_{10}-aryl, for example phenyl or naphthyl, C_7-C_{12}-aryl, for example phenylmethyl or phenylethyl,

R_1 and R_2 or R_1 and R_6 together are C_1-C_6-alkylene or C_3-C_8-1,2-cycloalkylene, or C_2-C_4-alkylene or C_3-C_8-cycloalkylene fused to 1,2-phenylene, and R_3 is as defined above,

R_2 and R_3 together are C_1-C_6-alkylene, C_1-C_8-alkylidene, C_3-C_8-1,2-cycloalkylene, C_3-C_8-cycloalkylidene, benzylidene, 1,2-phenylene, 1,2-pyridinylene, 1,2-naphthylene, or C_3-C_4-alkylene or C_3-C_8-1,2-cycloalkylene fused to 1,2-cycloalkylene or 1,2-phenylene, and R_1 is as defined above,

and R_1, R_2, R_3 and R_6 are each unsubstituted or substituted by one or more, identical or different radicals selected from the group of C_1-C_4-alkyl, C_2-C_4-alkenyl, C_1-C_4-alkoxy, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, C_1-C_4-alkoxymethyl or -ethyl, C_1-C_4-haloalkoxy, cyclohexyl, cyclohexyloxy, cyclohexylmethyl, cyclohexylmethyloxy, phenyl, phenyloxy, benzyl, benzyloxy, phenylethyl, phenylethyloxy, halogen, -OH, $-OR_4$, $-OC(O)R_4$, $-NH_2$, $-NHR_4$, $-NR_4R_5$, $-NH-C(O)-R_4$, $-NR_4-C(O)-R_4$, $-CO_2R_4$, $-CO_2-NH_2$, $-CO_2-NHR_4$, $-CO_2-NR_4R_5$ where R_4 and R_5 are each independently C_1-C_4-alkyl, cyclohexyl, cyclohexylmethyl, phenyl or benzyl.

[0007] The heterocyclic radicals are bonded via a ring carbon atom to the oxygen atoms or the carbon atom of the carbonyl groups in the compounds of the formulae I, II, III, IV and V.

[0008] Preferred substituents are methyl, ethyl, n- and i-propyl, n- and t-butyl, vinyl, allyl, methyloxy, ethyloxy, n- and i-propyloxy, n- and t-butyloxy, trifluoromethyl, trichloromethyl, β-hydroxyethyl, methoxy- or ethoxymethyl or -ethyl, trifluoromethoxy, cyclohexyl, cyclohexyloxy, cyclohexylmethyl, cyclohexylmethyloxy, phenyl, phenyloxy, benzyl, benzyloxy, phenylethyloxy, phenylethyl, halogen, -OH, $-OR_4$, $-OC(O)R_4$, $-NH_2$, $-NHR_4$, $-NR_4R_5$, $-NH-C(O)-R_4$, $-NR_4-C(O)-R_4$, $-CO_2R_4$, $-CO_2-NH_2$, $-CO_2-NHR_4$, $-CO_2-NR_4R_5$ where R_4 and R_5 are each independently C_1-C_4-alkyl, cyclohexyl, cyclohexylmethyl, phenyl or benzyl.

[0009] The aliphatic radical is preferably alkyl which may be linear or branched and preferably has 1 to 8, more preferably 1 to 4, carbon atoms, or preferably alkenyl or alkynyl, each of which may be linear or branched and preferably have 2 to 8, more preferably 2 to 4, carbon atoms. When R_2 and R_3 are alkenyl or alkynyl, the unsaturated bond is preferably in the β-position to the oxygen atom. Examples include methyl, ethyl, n- and i- propyl, n-, i- and t-butyl, pentyl, i-pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl, vinyl, allyl, ethynyl and propargyl. A preferred group of aliphatic radicals is methyl, ethyl, n- and i- propyl, n-, i- and t-butyl.

[0010] The cycloaliphatic radical is preferably cycloalkyl or cycloalkenyl having preferably 3 to 8, more preferably 5 or 6, ring carbon atoms. Some examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, and also cyclopentenyl, cyclohexenyl and cyclohexadienyl. Particular preference is given to cyclopentyl and cyclohexyl.

[0011] The heterocycloaliphatic radical is preferably heterocycloalkyl or heterocycloalkenyl having preferably 3 to 6 carbon atoms, 4 to 7 ring members and heteroatoms selected from the group of -O- and -NR'- where R' is H, C_1-C_8-alkyl, preferably C_1-C_4-alkyl, C_5- or C_6-cycloalkyl, C_6-C_{10}-aryl, for example phenyl or naphthyl, phenyl or phenylethyl. Some examples are pyrrolidinyl, pyrrolinyl, tetrahydrofuranyl, dihydrofuranyl and piperazinyl.

[0012] The cycloaliphatic-aliphatic radical is preferably cycloalkyl-alkyl or -alkenyl having preferably 3 to 8, more preferably 5 or 6, ring carbon atoms, and preferably 1 to 4, or 2-4, more preferably 1 or 2, or 2 or 3, carbon atoms in the alkyl group and alkenyl groups respectively. Examples include cyclopentyl- or cyclohexylmethyl or -ethyl and cyclopentyl- or cyclohexylethenyl.

[0013] The heterocycloaliphatic-aliphatic radical is preferably heterocycloalkyl-alkyl or -alkenyl having preferably 3 to 6 carbon atoms, 4 to 7 ring members and heteroatoms selected from the group of -O- and -NR'- where R' is H, C_1-C_8-alkyl, preferably C_1-C_4-alkyl, C_5- or C_6-cycloalkyl, C_6-C_{10}-aryl, for example phenyl or naphthyl, phenyl or phenylethyl, and preferably 1 to 4, more preferably 1 or 2, carbon atoms in the alkyl group and 2 to 4, more preferably 2 or 3, carbon atoms in the alkenyl group. Examples include pyrrolidinylmethyl or -ethyl or -ethenyl, pyrrolinylmethyl or -ethyl or -ethenyl, tetrahydrofuranylmethyl or -ethyl or -ethenyl, dihydrofuranylmethyl or -ethyl or -ethenyl, and piperazinylmethyl or -ethyl or -ethenyl.

[0014] The aromatic radicals are preferably naphthyl and in particular phenyl.

[0015] The aromatic-aliphatic radicals are preferably phenyl- or naphthyl-C_1-C_4-alkyl or -C_2-C_4-alkenyl. Some examples are benzyl, naphthylmethyl, β-phenylethyl and β-phenylethenyl.

[0016] The heteroaromatic radicals are preferably 5- or 6-membered, optionally fused ring systems. Some examples are pyridinyl, pyrimidinyl, pyrazinyl, pyrrolyl, furanyl, oxazolyl, imidazolyl, benzofuranyl, indolyl, benzimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl.

[0017] The heteroaromatic-aliphatic radicals are preferably 5- or 6-membered, optionally fused ring systems which are bonded via one of their carbon atoms to the free bond of an alkyl group or alkenyl group where the alkyl group preferably contains 1 to 4, more preferably 1 or 2, carbon atoms, and the alkenyl group preferably contains 2 to 4, more preferably 2 or 3, carbon atoms. Some examples are pyridinylmethyl or -ethyl or -ethenyl, pyrimidinylmethyl or -ethyl or -ethenyl, pyrrolyl methyl or -ethyl or -ethenyl, furanylmethyl or -ethyl or -ethenyl, imidazolylmethyl or -ethyl or -ethenyl, indolylmethyl or -ethyl or - ethenyl.

[0018] R_6 is preferably an aliphatic, cycloaliphatic or araliphatic radical, and more preferably linear C_1-C_4-alkyl.

[0019] More preferred compounds of the formulae I, II, III, IV and V include those where

R_1, R_2, R_3 and R_6 are each independently linear or branched C_1-C_8-alkyl, C_4-C_7-cycloalkyl or C_4-C_6-heterocycloalkyl having heteroatoms from the group of O and N, C_6-C_{10}-aryl or C_4-C_9-heteroaryl having heteroatoms from the group of O and N, C_4-C_7-cycloalkyl-C_1-C_4-alkyl or C_3-C_6-heterocycloalkyl-C_1-C_4-alkyl having heteroatoms from the group of O and N, C_6-C_{10}-aryl-C_1-C_4-alkyl or C_4-C_9-heteroaryl-C_1-C_4-alkyl having heteroatoms from the group of O and N,

R_1 and R_2 or R_1 and R_6 together are C_1-C_4-alkylene or C_4-C_7-1,2-cycloalkylene, or C_2-C_4-alkylene or C_4-C_7-cycloalkylene fused to 1,2-phenylene, and R_3 is as defined above,

R_2 and R_3 together are C_1-C_4-alkylene, C_1-C_4-alkylidene, C_4-C_7-1,2-cycloalkylene, C_4-C_7-cycloalkylidene, benzylidene, 1,2-phenylene, 1,2-pyridinylene, 1,2-naphthylene, or C_3-C_4-alkylene or C_4-C_7-cycloalkylene fused to 1,2-cycloalkylene or 1,2-phenylene, and R_1 is as defined above

where R_1, R_2, R_3 and R_6 are each unsubstituted or substituted by one or more, identical or different radicals selected from the group of C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, C_1-C_4-alkoxymethyl or -ethyl, C_1-C_4-haloalkoxy, cyclohexyl, cyclohexyloxy, cyclohexylmethyl, cyclohexylmethyloxy, phenyl, phenyloxy, benzyl, benzyloxy, phenylethyl, phenylethyloxy, halogen, -OH, $-OR_4$, $-OC(O)R_4$, $-NH_2$, $-NHR_4$, $-NR_4R_5$, $-NH-C(O)-R_4$, $-NR_4-C(O)-R_4$, $-CO_2R_4$, $-CO_2-NH_2$, $-CO_2-NHR_4$, $-CO_2-NR_4R_5$ where R_4 and R_5 are each independently C_1-C_4-alkyl, cyclohexyl, phenyl or benzyl.

[0020] A preferred subgroup of the compounds of the formulae I, II, III, IV and V are those where

R_1, R_2, R_3 and R_6 are each independently linear or branched C_1-C_4-alkyl, C_2-C_4-alkenyl, C_5-C_6-cycloalkyl, phenyl, phenylethenyl, C_5-C_6-cycloalkyl-C_1-C_2-alkyl, or C_6-C_{10}-aryl-C_1-C_2-alkyl,

R_1 and R_2 or R_1 and R_6 together are C_1-C_3-alkylene or C_5-C_6-1,2-cycloalkylene,

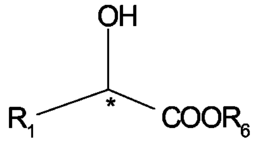
R_2 and R_3 together are C_2-C_4-alkylene, C_1-C_4-alkylidene, C_5-C_6-1,2-cycloalkylene, C_5-C_6-cycloalkylidene, benzyli-

dene, 1,2-phenylene
where R_1, R_2, R_3 and R_6 are each unsubstituted or substituted as defined previously.

[0021] A particularly preferred subgroup of the compounds of the formulae I, II, III, IV and V are those where
R_1 and R_6 are each C_1-C_4-alkyl, C_2-C_4-alkenyl, cyclohexyl, phenyl, benzyl, phenylethyl or phenylethenyl,
R_2 and R_3 are each independently linear or branched C_1-C_4-alkyl, cyclohexyl, phenyl, benzyl or phenylethyl,
R_1 and R_2 or R_1 and R_6 together are C_2-C_3-alkylene or 1,2-cyclohexylene,
R_2 and R_3 together are C_2-C_3-alkylene, C_1-C_4-alkylidene, 1,2-cyclohexylene, cyclohexylidene, benzylidene or 1,2-phenylene
where R_1, R_2, R_3 and R_6 are each unsubstituted or substituted by methyl, ethyl, n- and i-propyl, n- and t-butyl, vinyl, allyl, methyloxy, ethyloxy, n- and i-propyloxy, n- and t-butyloxy, trifluoromethyl, trichloromethyl, β-hydroxyethyl, methoxy- or ethoxymethyl or -ethyl, trifluoromethoxy, cyclohexyl, cyclohexyloxy, cyclohexylmethyl, cyclohexylmethyloxy, phenyl, phenyloxy, benzyl, benzyloxy, phenylethyloxy, phenylethyl, halogen, -OH, $-OR_4$, $-OC(O)R_4$, $-NH_2$, $-NHR_4$, $-NR_4R_5$, $-NH-C(O)-R_4$, $-NR_4-C(O)-R_4$, $-CO_2R_4$, $-CO_2-NH_2$, $-CO_2-NHR_4$, $-CO_2-NR_4R_5$ where R_4 and R_5 are each independently C_1-C_4-alkyl, cyclohexyl, cyclohexylmethyl, phenyl or benzyl.

[0022] Some of the compounds of the formulae I, II, III, IV and V are known or can be prepared in a manner known per se by means of similar processes.

[0023] The compounds of the formulae I, II, III, IV and V are hydrogenated to chiral secondary alcohols of the formulae VI, VII, VIII and IX



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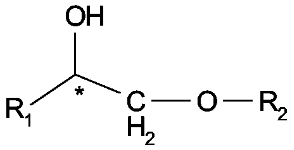

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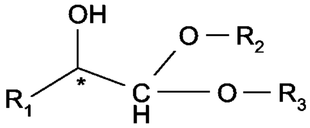

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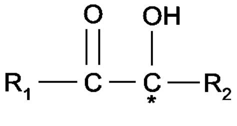

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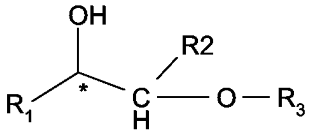
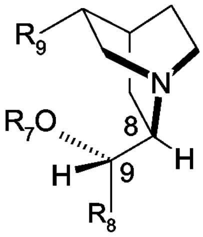

(X)

where R_1, R_2, R_3 and R_6 are each as previously defined and the symbol * represents predominantly the S-form of one of the stereoisomers.

[0024] Platinum catalysts are known, extensively described and commercially available. It is possible to use either platinum in metal form, for example as a powder, or, which is preferred, platinum metal applied to finely divided supports. Examples of suitable supports include carbon, metal oxides, for example SiO_2, TiO_2, Al_2O_3, metal salts, and natural or synthetic silicates. The catalyst may also be a platinum colloid. The amount of platinum metal on the support may be, for example, 1 to 10% by weight, preferably 3 to 8% by weight, based on the support. Before their use, the catalysts may be activated by treating with hydrogen at elevated temperature and/or with ultrasound. Preferred catalysts are platinum on Al_2O_3.

[0025] The cinchonines unsubstituted in the 3-position, 3-ethylidenyl- or 9-methoxycinchonines or derivatives thereof to be used according to the invention may, for example, correspond to the formula XI with 8(R),9(S)-configuration


(XI),

where

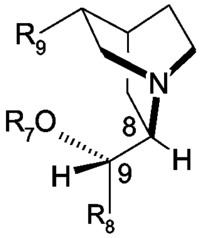
R_9 is CH_2=CH- or CH_3CH_2- and R_7 is methyl, or

R_9 is H or CH_3-CH= and R_7 is H or methyl, and

R_8 is unsubstituted or C_1-C_4-alkyl- or C_1-C_4-alkoxy-substituted C_6-C_{14}-aryl or C_5-C_{13}-heteroaryl having heteroatoms selected from the group of -N=, -O-, -S- and -N(C_1-C_4-alkyl)-.

[0026] R_8 as aryl and heteroaryl may be a monocyclic or fused polycyclic radical having preferably 2 or three rings. The rings preferably contain 5 or 6 ring members. Some examples are phenyl, furyl, thiophenyl, N-methylpyrrolyl, pyridinyl, naphthyl, tetrahydronaphthyl, anthracenyl, phenanthryl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, indenyl, fluorenyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, dihydrobenzothiophenyl, N-methylindolyl, dihydro-N-methylindolyl, dibenzofuranyl, dibenzothiophenyl and N-methylcarbazolyl.

[0027] The cinchonines unsubstituted in the 3-position, 3-ethylidenyl- or 9-methoxycinchonines or derivatives thereof to be used according to the invention preferably correspond to the formula XIa with 8(R),9(S)-configuration

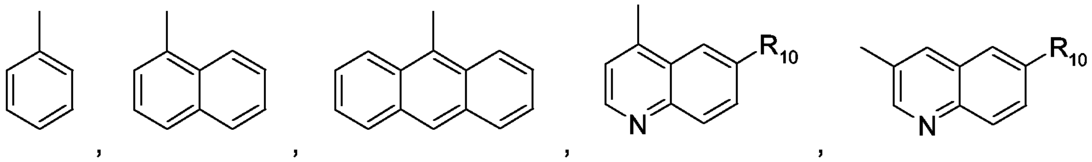

(XIa),

where

R_9 is CH_2=CH- or CH_3CH_2- and R_7 is methyl, or

R_9 is H or CH_3-CH= and R_7 is H or methyl,

R_8 is a radical of the formulae



and R_{10} is H, OH or C_1-C_4-alkoxy.

[0028] R_{10} is preferably H, OH or methoxy.

[0029] The compounds of the formula XI where R_9 is CH_2=CH- or CH_3CH_2- and R_7 is methyl may be prepared in a simple manner by methylating the hydroxyl group bonded to C9 of appropriate natural cinchona alkaloids. Compounds where R_9 is ethyl are obtainable by hydrogenating the R_9 vinyl group.

[0030] The compounds of the formula XI where R_9 is CH_3-CH= may be prepared by isomerizing the R_9 vinyl group in the presence of metal complexes, for example ruthenium/phosphine complexes. An implementation of the process is described in the examples. In general, mixtures of the Z- and E-isomers are obtained which can be used directly as such.

[0031] The compounds of the formula XI which are not derived from natural cinchonines are synthetically accessible, for example, by means of reacting quinuclidine N-oxide with lithium alkyls (Li-methyl or Li-n-butyl) with aldehydes R_8-CH=O, subsequent reaction with a Lewis acid, for example $TiCl_3$, and ensuing alkaline hydrolysis. The diastereomers may be separated chromatographically on silica gel, and the enantiomers may be separated chromatographically on chiral columns. This is described in more detail in the examples.

[0032] The platinum metal may be used, for example, in an amount of 0.01 to 10% by weight, preferably 0.05 to 10% by weight and more preferably 0.1 to 5% by weight, based on the prochiral ketone used, although amounts of 0.1 to 3% by weight, or 0.1 to 1% by weight generally suffice. The increased activity of the hydrogenation system to be used according to the invention allows smaller total amounts of catalyst, which makes the process more economic.

[0033] The modifier may be used, for example, in an amount of 0.1 to 10 000% by weight, preferably 1 to 500% by weight and more preferably 10 to 200% by weight, based on the platinum metal used. The modifier may be introduced into the reaction vessel together with the platinum metal catalyst, or the platinum metal catalyst may be impregnated beforehand with the modifier.

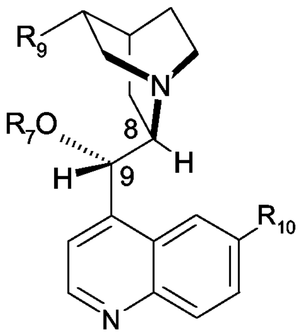
[0034] The hydrogenation is preferably carried out under a hydrogen pressure of up 200 bar, more preferably up to 150 bar and particularly preferably 10 to 100 bar.

[0035] The reaction temperature may be, for example, -50 to 100°C, more preferably 0 to 50°C and particularly preferably 0 to 35°C. It is generally possible to achieve better enantioselectivies at low temperatures.

[0036] The reaction may be carried out without or in an inert solvent or mixtures of solvents. Examples of suitable solvents include aliphatic, cycloaliphatic and aromatic hydrocarbons (pentane, hexane, petroleum ether, cyclohexane, methylcyclohexane, benzene, toluene, xylene), ethers (diethyl ether, dibutyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, tetrahydrofuran, dioxane), water, alcohols (methanol, ethanol, propanol, butanol, ethylene glycol, diethylene glycol, ethylene glycol monomethyl or monoethyl ether, diethylene glycol monomethyl or monoethyl ether), ketones (acetone, methyl isobutyl ketone), carboxylic esters and lactones (ethyl or methyl acetate, valerolactone), N-substituted carboxamides and lactams (dimethylformamide, N-methylpyrrolidone), and carboxylic acids (acetic acid, propionic acid, butyric acid). The choice of the solvent may be used to influence the optical yield. For example, aromatic hydrocarbons (benzene, toluene, xylene) have proven particularly useful in the case of α-ketoacetals and aromatic α-ketocarboxylic esters, while better results can be achieved using carboxylic acids, for example acetic acid, in the case of aliphatic α-ketocarboxylic acids.

[0037] The process according to the invention may, for example, be carried out in such a way that the catalyst is initially charged in an autoclave with the nitrogen base, optionally with a solvent, then the prochiral α-ketone is added, then the air is displaced with an inert gas, for example noble gases, hydrogen is injected in and then the reaction is started, optionally with stirring or shaking, and hydrogenation is effected until no more hydrogen takeup is observed. The α-hydroxyl compound formed may be isolated and purified by customary methods, for example distillation, crystallization and chromatographic methods.

[0038] The invention also provides compounds of the formula XIb



(XIb),

where

R_9 is CH_2=CH- or CH_3CH_2- and R_7 is methyl, or
R_9 is H or CH_3-CH= and R_7 is H or methyl, and
R_{10} is H or C_1-C_4-alkoxy.

[0039] When R_7 is H, R_{10} = H and R_9 is CH_2=CH-, the molecule is cinchonine (Cn) and when R_7 is H, R_{10} = H and R_9 is CH_3CH_2-, the molecule is hydrocinchonine (HCn).

[0040] The (S)-α-alcohols which can be prepared according to the invention are valuable intermediates for the preparation of natural active ingredients (B. T. Cho et al. in Tetrahedron: Asymmetry Vol. 5, No. 7 (1994), pages 1147 to 1150), and synthetic active pharmaceutical ingredients and pesticides. The (S)-α-alcohols obtainable may be converted beforehand by known processes to derivatives which may then be used as intermediates for the preparation of active ingredients. The acid hydrolysis of, for example, α-ketoacetals leads to 1,4-dioxanes or the corresponding aldehydes which are either hydrogenated to 1,2-diols having a secondary opticallly active hydroxyl group, or reacted with amines in the presence of phenylboric acids to optionally substituted optically active 1-phenyl-1-amino-2-hydroxyalkanes. After the protection of the OH group, for example by reaction with benzyl bromide, the hydroxyl-protected aldehydes may be obtained by reacting with strong acids and may be hydrogenated to 1,2-diols or converted to S-α-hydroxycarboxylic acids by oxidation (for example with chromium trioxide) and removing the protecting group.

[0041] The examples which follow illustrate the invention in detail. The optical yield is determined by gas chromatography using a Supelco Beta-dex column (article No. 2-4301), hydrogen as the carrier gas and elevated temperatures; or by means of HPLC (Chiracel OD column, using 95:5 hexane/isopropanol). The conversion is determined by means of ^{1}H NMR.

A) Preparation of modifiers

Example A1: Preparation of O-methylcinchonine (MeO-Cn, R_7 in formula XIb = methyl, R_{10} = H, R_9 = CH_2=CH-)

[0042] 0.60 g of potassium hydride (15.0 mmol) is weighed into a 250 ml two-necked flask equipped with a reflux condenser and dropping funnel under argon. This is washed three times with absolute n-pentane and subsequently suspended in 50 ml of absolute tetrahydrofuran. 3.24 g (11.0 mmol) of cinchonine (Cn) are then added in portions with ice cooling, and obvious gas development can be observed. After completion of addition, stirring is continued at 0°C for about another half hour until an almost clear orange solution is obtained. The solution is then heated to 50°C for a further 2 hours until no more gas development can be detected. At room temperature (RT), 0.69 ml (1.56 g; 11.0 mmol) of iodomethane are then slowly added dropwise. The solution is stirred at RT for 12 hours and then hydrolyzed using 50 ml of H_2O with ice cooling. The organic and the aqueous phases are separated, and the aqueous phase is extracted three times more with ethyl acetate (EA). The combined organic phases are dried over $MgSO_4$ and concentrated on a rotary evaporator (RE). Chromatographic purification on a silica gel column (EA / $Nethyl_3$ 9:1) and drying under high vacuum give 2.82 g (83%) of the title compound as a pale yellow solid. Recrystallization from a little n-hexane provides 2.50 g (74%) of colourless, rhombic crystals. Melting point: 113-114°C; $[\alpha]_D^{20}$: + 242 ° (c = 0.90, $CHCl_3$).

Example A2: Preparation of O-methylquinidine (MeO-Qd, R_7 in formula XIb = methyl, R_{10} = Omethyl, R_9 = CH_2=CH-)

[0043] The procedure of Example A1 is followed using quinidine. The title compound is obtained in a yield of 71% as a yellow, viscous oil. $[\alpha]_D^{20}$: + 202 ° (c = 0.78, $CHCl_3$).

Example A3: Preparation of (E)/(Z)-isocinchonine (iso-Cn, R_7 in formula XIb = H, R_{10} = H, R_9 = CH_3-CH=).

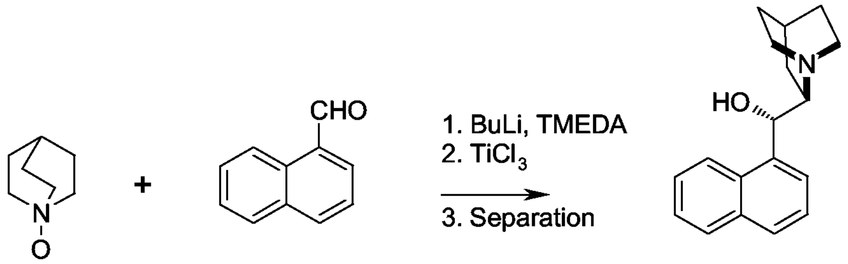
[0044] In a 100 ml two-necked flask equipped with a reflux condenser, 106.0 mg (408 μmol) of triphenylphosphine and 25.0 mg (100 μmol) of $RuCl_3 \cdot nH_2O$ in 30 ml absolute dimethylformamide under argon are heated to 150°C until a clear orange solution is formed (approx. 15 minutes). The solution is subsequently allowed to cool to 100°C, then 2 g (6.8 mmol) of cinchonine are added and the solution is heated once again to 150°C for half an hour. The still-hot reaction mixture is poured into 100 ml of precooled water and stirred at 5°C for 1 hour. The precipitated colourless solid is filtered off and dried under high vacuum. After recrystallization from dimethoxyethane, 1.10 g (55%) of the title compound as an inseparable 1:1 mixture of the Z- and E-isomers are obtained in the form of fine, colourless needles. Melting point of the diastereomer mixture: 229-231°C; $[\alpha]_D^{20}$: + 173 ° (c = 0.93, $CHCl_3$).

Example A4: Preparation of (E)/(Z)-apoisoquinidine (iso-Qd, R_7 in the formula XIb = H, R_{10} = Omethyl, R_9 = CH_3-CH=).

[0045] The procedure of Example A3 is followed using quinidine. For isolation, the reaction mixture after aqueous workup is initially adjusted to a pH of 9-10 using 1 M NaOH solution and then extracted repeatedly with methylene chloride. The combined organic phases are concentrated under high vacuum and then the residue is recrystallized from diethyl ether. The title compound is obtained as an inseparable 1:1 mixture of the Z- and E-isomers in the form of a beige solid. Melting point of the diastereomer mixture: 161-165°C; $[\alpha]_D^{20}$: + 148 ° (c = 0.88, $CHCl_3$).

Example A5: Preparation of rubanol, R_7 in formula XIa = H, R_9 = H, R_8 = naphthyl

[0046]



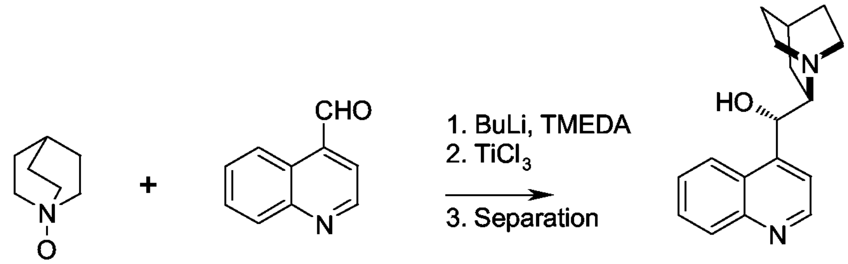
BuLi: n-butyllithium; TMEDA: tetramethylethylenediamine.

[0047] 3.58 ml (5.7 mmol) of *n*-butyllithium (1.6 M in *n*-hexane) are added dropwise at -78°C within 30 min to a solution of 0.66 g (5.2 mmol) of azabicyclo[2.2.2]octane N-oxide and 0.86 ml (0.67 g; 5.7 mmol) of TMEDA in 30 ml of absolute THF. The yellow reaction solution is stirred at -78°C for 1 h. 0.78 g (5.0 mmol) of α-naphthaldehyde in 10 ml of absolute tetrahydrofuran is then added slowly. Stirring is continued at -78°C for 2 h and the mixture is then subsequently heated within 12 h to room temperature (RT). After adding 10 ml of saturated, aqueous NH_4Cl solution, the mixture is stirred at RT for 30 minutes.

[0048] The reduction of the *N*-oxide to the tertiary amine is carried out in situ using $TiCl_3$ solution (1.9 M in 2.0 M aqueous HCl) without further workup. Titanium(*III*) hydrochloric acid solution is added with ice cooling until a deep violet colour remains even after prolonged stirring. After heating to RT, the reaction mixture is set to pH = 10 using 15 per cent aqueous NaOH solution. The precipitated salts are filtered through Celite, and the filtrate is repeatedly extracted using ethyl acetate. The combined organic phases are washed with saturated aqueous NaCl solution, dried over potassium carbonate, filtered and concentrated on a rotary evaporator. The ^1H NMR spectrum of the crude product shows that the two diastereomers are formed in a 1:1 ratio. Chromatographic purification on a silica gel column (ethyl acetate/triethyiamine, 9:1) provides 0.55 g (41%) of the desired *erythro*-isomer as colourless needles. Preparative HPLC (Daicel Chiralcel OD®, 20 x 250 mm, n-hexane/isopropanol, 95:5, 1% of diethylamine), 20.0 ml/min, t_r[(-)-enantiomer] = 10.4 min, t_r[(+)-enantiomer] = 15.9 min) separates the two *erythro*-enantiomers to 98% ee in each case. ^1H NMR ($CDCl_3$, 400 MHz): 8.06 (d, 1H, ^3J = 8.2 Hz), 7.86 (dd, 1H, ^3J = 7.8 Hz, ^4J = 1.5 Hz), 7.76 (d, 1H, ^3J = 8.2 Hz), 7.71 (d, 1H, ^3J = 7.1 Hz), 7.48-7.41 (m, 3H), 5.77 (d, 1H, ^3J = 4.6 Hz), 3.58-2.52 (m, 6H), 1.91-1.31 (m, 7H). ^{13}C NMR ($CDCl_3$, 101 MHz): 139.7 (q), 133.8 (q), 130.5 (q), 128.9 (t), 127.8 (t), 126.0 (t), 125.4 (2x t), 123.4 (t), 123.2 (t), 72.9 (t), 60.1 (t), 50.7 (s), 43.9 (s), 26.6 (s), 26.5 (s), 25.8 (s), 22.1 (t). Melting point: 202-204°C. $[\alpha]_D^{20}$- 135° (c = 0.35, $CHCl_3$).

Example A6: Preparation of EXN-1, R_7 in formula XIa = H, R_9 = H, R_8 = quinolinyl

[0049]



[0050] The synthesis is carried out in a similar manner to Example A5 using 3.58 g (28.2 mmol) of azabicyclo[2.2.2] octane *N*-oxide, 4.70 ml (31.1 mmol) of TMEDA, 20.00 ml (32.0 mmol) of *n*-butyllithium (1.6 M in *n*-hexane) and 5.00 g (31.7 mmol) of quinoline-4-carbaldehyde. The ^1H NMR spectrum of the crude product shows that the two diastereomers are formed in a 1:1 ratio. Chromatographic purification on a silica gel column (ethyl acetate/triethylamine, 9:1) provides 2.95 g (39%) of rubanol as a colourless solid. Semipreparative HPLC (Chiracel OD-H®, n-heptane / isopropanol 98:2, 0.5 ml/min, t_r[(-)-rubanol] = 52.1 min, tr[(+)-rubanol] = 63.8 min) separates the *erythro*-enantiomers from each other to 99% ee in each case. ^1H NMR ($CDCl_3$, 400 MHz): 8.90 (d, 1H, ^3J = 4.6 Hz), 8.12 (dd, 1H, ^3J = 8.6 Hz, ^4J = 0.8 Hz), 7.97 (d, 1H, ^3J = 8.4 Hz), 7.69-7.64 (m, 2H), 7.43 (dt, 1H, ^3J = 7.0 Hz, ^4J = 1.2 Hz), 5.78 (d, 1H, ^3J = 3.5 Hz), 4.70 (br, 1H), 3.57-3.52 (m, 1H), 3.14-2.49 (m, 4H), 1.89-1.27 (m, 7H). ^{13}C NMR ($CDCl_3$, 101 MHz): 150.6 (q), 148.7 (t), 148.4 (q), 130.8 (t), 129.4 (t), 126.9 (t), 126.1 (t), 125.5 (q), 123.4 (t), 118.7 (t), 72.0 (t), 60.4 (t), 51.1 (s), 44.3 (s), 26.7 (s), 26.3 (s), 25.9 (s), 22.3 (t). Melting point: 222-224°C. $[\alpha]_D^{20}$: + 99° (c = 0.51, $CHCl_3$).

B) Hydrogenations of prochiral α-ketones

Examples B1-B8: Hydrogenation of methyl pyruvate [CH_3-C(O)-$COOC_2H_5$] to ethyl (2S)-hydroxypropionate

[0051] In a 2 ml microanalysis bottle equipped with a magnetic stirrer, 10 mg of 5% Pt/Al_2O_3 (catalyst JMC 94, batch 14017/01, pretreated under hydrrogen at 400°C for 2 hours) are initially charged and admixed with 1 mg of modifier. 100 microlitres of ethyl pyruvate dissolved in 1 ml of solvent are then added, and the microanalysis bottle is then placed in a 50 ml pressure autoclave together with three further microanalysis bottles. The autoclave is purged three times with argon and three times with hydrogen and then 60 bar of hydrogen are injected in. The reactions are started by switching on the magnetic stirrer and carried out at room temperature. After 60 to 70 minutes, the pressure is dissipated, and the autoclave is purged three times with argon and opened. The catalysts are filtered off and the reaction mixture is analysed. The results are reported in Table 1.

Table 1:

[Abbreviations: AcOH is acetic acid]				
Example No.	Modifier	Solvent	ee (%)	Conversion (%)
B1	MeO-Cn	AcOH	85	100
B2	MeO-Qd	AcOH	90	100
B3	iso-Cn	AcOH	88	100
B4	iso-Qd	AcOH	84	100
B5	EXN-1	AcOH	88	100
B6	rubanol	AcOH	82	100
Comparative	Cn	AcOH	88	>99
Comparative	HCn	AcOH	88	>99

Table 1: (continued)

[Abbreviations: AcOH is acetic acid]

Example No.	Modifier	Solvent	ee (%)	Conversion (%)
B7	MeO-Cn	toluene	31	100
B8	MeO-Qd	toluene	53	100
B9	iso-Cn	toluene	74	100
B10	iso-Qd	toluene	61	100
B11	EXN-1	toluene	69	100
B12	rubanol	toluene	67	100
Comparative	Cn	toluene	68	>99
Comparative	HCn	toluene	65	>99

Examples B13 - B24: Hydrogenation of methyl phenylketoacetate

[0052] The procedure of Example B1 is followed using methyl phenylketoacetate. The results are reported in Table 2.

Table 2:

Example No.	Modifier	Solvent	ee (%)	Conversion (%)
13	MeO-Cn	AcOH	18	100
B14	MeO-Qd	AcOH	15	100
B15	iso-Cn	AcOH	75	100
B16	iso-Qd	AcOH	15	100
B17	EXN-1	AcOH	53	100
B18	rubanol	AcOH	37	100
Comparative	HCn	AcOH	51	100
B19	MeO-Cn	toluene	31	100
B20	MeO-Qd	toluene	8	100
B21	iso-Cn	toluene	80	100
B22	iso-Qd	toluene	66	100
B23	EXN-1	toluene	70	100
B24	rubanol	toluene	90	100
Comparative	HCn	toluene	78	100

Examples B25-B36: Hydrogenation of methylglyoxal 1,1-dimethyl acetal

[0053] The procedure of Example B1 is followed using methylglyoxal 1,1-dimethyl acetal. The results are reported in Table 3.

Table 3:

Example No.	Modifier	Solvent	ee (%)	Conversion (%)
B25	MeO-Cn	AcOH	93	100
B26	MeO-Qd	AcOH	92	100
B27	iso-Cn	AcOH	82	97
B28	iso-Qd	AcOH	81	100

Table 3: (continued)

Example No.	Modifier	Solvent	ee (%)	Conversion (%)
B29	EXN-1	AcOH	84	100
B30	rubanol	AcOH	69	100
Comparative	Cn	AcOH	76	94
Comparative	HCn	AcOH	78	96
B31	MeO-Cn	toluene	19	71
B32	MeO-Qd	toluene	29	77
B33	iso-Cn	toluene	42	79
B34	iso-Qd	toluene	26	55
B35	EXN-1	toluene	19	100
B36	rubanol	toluene	72	100
Comparative	Cn	toluene	33	55
Comparative	HCn	toluene	20	65

Examples B37-B48: Hydrogenation of ethyl 2,4-diketobutyrate to ethyl (S)-4-keto-2-hydroxybutyrate

[0054] The procedure of Example B1 is followed using ethyl 2,4-diketobutyrate. The results are reported in Table 4.

Table 4:

Example No.	Modifier	Solvent	ee (%)	Conversion (%)
B37	MeO-Cn	AcOH	59	100
B38	MeO-Qd	AcOH	73	100
B39	iso-Cn	AcOH	67	100
B40	iso-Qd	AcOH	60	100
B41	EXN-1	AcOH	74	98
B42	rubanol	AcOH	61	96
Comparative	HCn	AcOH	64	100
B43	MeO-Cn	toluene	43	100
B44	MeO-Qd	toluene	31	90
B45	iso-Cn	toluene	70	100
B46	iso-Qd	toluene	66	93
B47	EXN-1	toluene	66	100
B48	rubanol	toluene	35	100
Comparative	HCn	toluene	64	100

Examples B49-B60: Hydrogenation of ethyl 2,4-dioxo-4-phenylbutyrate to ethyl (S)-4-keto-4-phenyl-2-hydroxybutyrate

[0055] The procedure of Example B1 is followed using ethyl 2,4-dioxo-4-phenylbutyrate. The results are reported in Table 5.

Table 5:

Example No.	Modifier	Solvent	ee (%)	Conversion (%)
B49	MeO-Cn	AcOH	62	100

Table 5: (continued)

Example No.	Modifier	Solvent	ee (%)	Conversion (%)
B50	MeO-Qd	AcOH	61	100
B51	iso-Cn	AcOH	62	97
B52	iso-Qd	AcOH	61	100
B53	EXN-1	AcOH	74	100
B54	rubanol	AcOH	61	100
Comparative	HCn	AcOH	64	100
B55	MeO-Cn	toluene	18	100
B56	MeO-Qd	toluene	4	100
B57	iso-Cn	toluene	71	99
B58	iso-Qd	toluene	4	10
B59	EXN-1	toluene	53	100
B60	rubanol	toluene	62	100
Comparative	HCn	toluene	64	100

Examples B61-B71: Hydrogenation of ethyl 4-phenyl-2-oxobutyrate

[0056] The procedure of Example B1 is followed using ethyl 4-phenyl-2-oxobutyrate. The results are reported in Table 6.

Table 6:

Example No.	Modifier	Solvent	ee (%)	Conversion (%)
B61	MeO-Cn	AcOH	81	100
B62	MeO-Qd	AcOH	82	100
B63	iso-Cn	AcOH	81	100
B64	iso-Qd	AcOH	76	100
B65	EXN-1	AcOH	86	100
B66	rubanol	AcOH	78	100
Comparative	HCn	AcOH	78	100
B67	MeO-Cn	toluene	16	100
B68	MeO-Qd	toluene	racemic	100
B68	iso-Cn	toluene	66	100
B69	iso-Qd	toluene	55	100
B70	EXN-1	toluene	46	100
B71	rubanol	toluene	64	100
Comparative	HCn	toluene	57	>95

Example B72 and comparative example: Hydrogenation of ethyl pyruvate

[0057] 5 mg of modifier are initially charged in a 50 ml pressure autoclave equipped with a magnetic stirrer and baffle. 50 mg of catalyst (JMC 94, batch 14017/01, pretreated under hydrogen at 400°C for 2 h) are slurried in 2 ml of acetic acid and transferred to the autoclave. The substrate is dissolved in the rest of the solvent (total 20 ml) and likewise transferred to the autoclave. The autoclave is purged three times with argon and three times with hydrogen and then

60 bar of hydrogen are injected in. The reaction is started by switching on the magnetic stirrer. The temperature is kept constant at 25°C with the aid of a cryostat. The pressure in the autoclave is kept constant during the reaction using a dome pressure regulator, and the hydrogen takeup in the reactor is measured by the pressure decrease in a reservoir. After the end of the reaction, the reactor is decompressed, and the autoclave is purged three times with argon and then opened. The catalyst is filtered off. The conversion is determined by gas chromatography. The results are reported in Table 7. HCn means 10,11-dihydrocinchonine.

Table 7:

Example	Modifier	Time (min)	Conversion (%)	ee (%)	mmol of H_2 / g of
Comparative	HCn	19	100	89	148
B72	A3	16	100	91	182

Example B73 and comparative example: Hydrogenation of methylglyoxal 1,1-dimethyl acetal

[0058] The procedure is the same as in Example B72. The conversion is determined by gas chromatography. The results are reported in Table 8. HCn means 10,11-dihydrocinchonine.

Table 8:

Example	Modifier	Time (min)	Conversion (%)	ee (%)	mmol of H_2 / g of catalyst
Comparative	HCn	120	51	71	24
B73	A3	120	61	79	35

Examples B74-B75 and comparative example: Hydrogenation of ethyl 4-phenyl-2,4-dioxobutyrate

[0059] The procedure is the same as in Example B72. The conversion is determined by gas chromatography. The results are reported in Table 9. HCn means 10,11-dihydrocinchonine

Table 9:

Example	Amount of catalyst	Modifier (amount in	Time (min)	Conversion (%)	ee (%)	mmol/g*min
Comparative	10 mg	HCn (2)	95	95	56	--
B74	125 mg	A3 (13)	60	94	78	6.72
B75	84 g	A3 (8400)	90	99	79	2.7

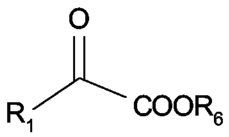
Claims

1. Process for enantioselectively hydrogenating prochiralen ketones to (S)-alcohols using platinum catalysts in the presence of cinchonines or quinidines as modifiers and in the presence of hydrogen, **characterized in that** modifiers are used which are selected from the group of cinchonines unsubstituted in the 3-position, 3-ethylidenyl- or 9-methoxycinchonines or derivatives thereof in which the quinoline ring is replaced by other rings.

2. Process according to Claim 1, **characterized in that** the prochiral α-ketones are saturated or unsaturated, open-chain or cyclic compounds which contain 5 to 30 carbon atoms which are unsubstituted or substituted by radicals which are stable under the hydrogenation conditions, and the carbon chain is uninterrupted or interrupted by heteroatoms from the group of -O-, =N- and -NR'- where R' is H, C_1-C_8-alkyl, C_5-C_8-cycloalkyl, C_6-C_{10}-aryl or C_7-C_{12}-aralkyl.

3. Process according to Claim 2, **characterized in that** the prochiral ketones are α-ketocarboxylic acids, α-ketocarboxylic esters, α-ketoethers, α-ketoacetals and α,β-diketones.

4. Process according to Claim 3, **characterized in that** the prochiral ketones correspond to the formulae I, II, III, IV and V



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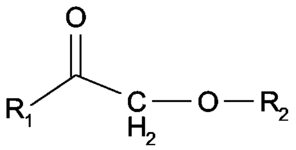

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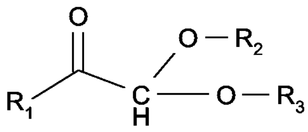

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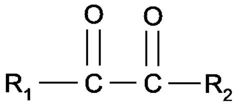

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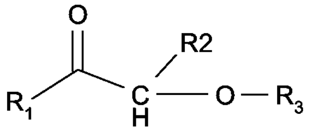


(V)

where

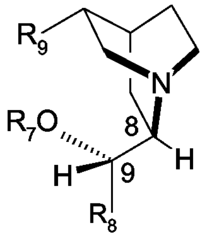
R_1, R_2, R_3 and R_6 are each independently a monovalent, saturated or unsaturated aliphatic radical having 1 to 12 carbon atoms, a saturated or unsaturated cycloaliphatic radical having 3 to 8 carbon atoms, a saturated or unsaturated heterocycloaliphatic radical having 3 to 8 ring members and one or two heteroatoms from the group of O, N and NR', a saturated or unsaturated cycloaliphatic-aliphatic radical having 4 to 12 carbon atoms, a saturated or unsaturated heterocycloaliphatic-aliphatic radical having 3 to 12 carbon atoms and one or two heteroatoms from the group of O, N and NR', an aromatic radical having 6 to 10 carbon atoms, a heteroaromatic radical having 4 to 9 carbon atoms and one or two heteroatoms from the group of O and N, an aromatic-aliphatic radical having 7 to 12 carbon atoms or a heteroaromatic-aliphatic radical having 5 to 11 carbon atoms and one or two heteroatoms from the group of O and N where R' is H, C_1-C_8-alkyl, preferably C_1-C_4-alkyl, C_5- or C_6-cycloalkyl, C_6-C_{10}-aryl, for example phenyl or naphthyl, C_7-C_{12}-aryl, for example phenylmethyl or phenylethyl,

R_1 and R_2 or R_1 and R_6 together are C_1-C_6-alkylene or C_3-C_8-1,2-cycloalkylene, or C_2-C_4-alkylene or C_3-C_8-cycloalkylene fused to 1,2-phenylene, and R_3 is as defined above,

R_2 and R_3 together are C_1-C_6-alkylene, C_1-C_8-alkylidene, C_3-C_8-1,2-cycloalkylene, C_3-C_8-cycloalkylidene, benzylidene, 1,2-phenylene, 1,2-pyridinylene, 1,2-naphthylene, or C_3-C_4-alkylene or C_3-C_8-1,2-cycloalkylene fused

to 1,2-cycloalkylene or 1,2-phenylene, and R_1 is as defined above,
and R_1, R_2, R_3 and R_6 are each unsubstituted or substituted by one or more, identical or different radicals selected from the group of C_1-C_4-alkyl, C_2-C_4-alkenyl, C_1-C_4-alkoxy, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, C_1-C_4-alkoxymethyl or -ethyl, C_1-C_4-haloalkoxy, cyclohexyl, cyclohexyloxy, cyclohexylmethyl, cyclohexylmethyloxy, phenyl, phenyloxy, benzyl, benzyloxy, phenylethyl, phenylethyloxy, halogen, -OH, $-OR_4$, $-OC(O)R_4$, $-NH_2$, $-NHR_4$, $-NR_4R_5$, $-NH-C(O)-R_4$, $-NR_4-C(O)-R_4$, $-CO_2R_4$, $-CO_2-NH_2$, $-CO_2-NHR_4$, $-CO_2-NR_4R_5$
where R_4 and R_5 are each independently C_1-C_4-alkyl, cyclohexyl, cyclohexylmethyl, phenyl or benzyl.

5. Process according to Claim 1, **characterized in that** cinchonines unsubstituted in the 3-position, 3-ethylidenyl- or 9-methoxycinchonines or derivatives thereof correspond to compounds of the formula XI with 8(R),9(S)-configuration



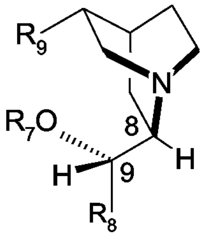
(XI),

where
R_9 is CH_2=CH- or CH_3CH_2- and R_7 is methyl, or
R_9 is H or CH_3-CH= and R_7 is H or methyl, and
R_8 is unsubstituted or C_1-C_4-alkyl- or C_1-C_4-alkoxy-substituted C_6-C_{14}-aryl or C_5-C_{13}-heteroaryl having heteroatoms selected from the group of -N=, -O-, -S- and -N(C_1-C_4-alkyl)-.

6. Process according to Claim 5, **characterized in that** R_8, as aryl and heteroaryl, is a monocyclic or fused polycyclic radical.

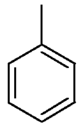
7. Process according to Claim 6, **characterized in that** aryl and heteroaryl comprise rings having 5 or 6 ring members.

8. Process according to Claim 5, **characterized in that** the cinchonines unsubstituted in the 3-position, 3-ethylidenyl- or 9-methoxycinchonines or derivatives thereof preferably correspond to compounds of the formula XIa with 8(R), 9(S)-configuration



(XIa),

where
R_9 is CH_2=CH- or CH_3CH_2- and R_7 is methyl, or
R_9 is H or CH_3-CH= and R_7 is H or methyl,
R_8 is a radical of the formulae



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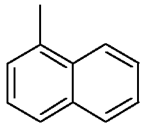

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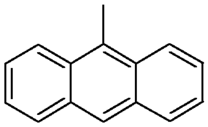

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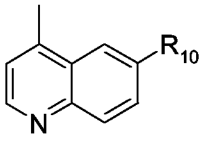

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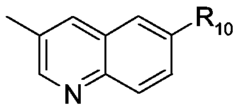


and R_{10} is H, OH or C_1-C_4-alkoxy.

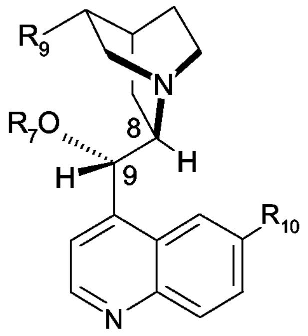
9. Process according to Claim 1, **characterized in that** the platinum metal is used in an amount of 0.01 to 10% by weight, based on the prochiral ketone used.

10. Process according to Claim 1, **characterized in that** the modifier is used in an amount of 0.1 to 10 000% by weight, based on the platinum metal used.

11. Process according to Claim 1, **characterized in that** the hydrogenation is carried out under a hydrogen pressure of up to 200 bar.

12. Process according to Claim 1, **characterized in that** the reaction temperature is -50 to 100°C.

13. Compounds of the formula XIb



(XIb),

where
R_9 is CH_2=CH- or CH_3CH_2- and R_7 is methyl, or
R_9 is H or CH_3-CH= and R_7 is H or methyl, and
R_{10} is H or C_1-C_4-alkoxy.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 03 10 0905

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	14 July 2003	Lauro, P

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X	DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; retrieved from XFIRE, accession no. 3920396 XP002247503 * abstract * & RABE; HAGEN : CHEM. BER. , vol. 74, 1941, page 636 -----	13	
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14-07-2003

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